RiskChallenge 2017

A risk assessment exercise

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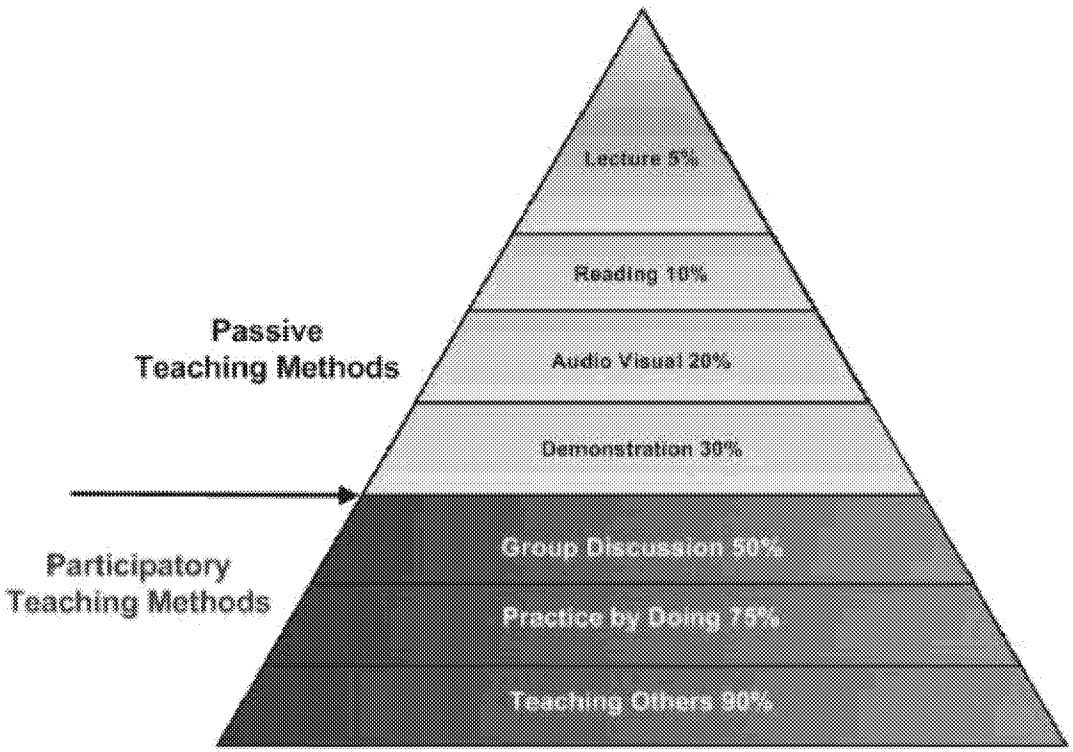
Today's Agenda (4hrs total)

- Background (5 min)
- Introducing risk assessment (45 min)
- Scenario description (10 min)
- Team exercise in decision-making: (120 min)
  - by assessing the risk of a chemical; and
  - choosing appropriate risk-management measures, if needed
- Debrief (60 min)

Intent and underlying principle

- Create a risk assessment participatory exercise
  - Adopted from "EcoChallenge" developed by AIHC members
- The learning pyramid and percent of retention:



http://thepeakperformancecenter.com/educational-learning/learning/principles-of-learning/learning-pyramid/

Format, premise, and level

Format

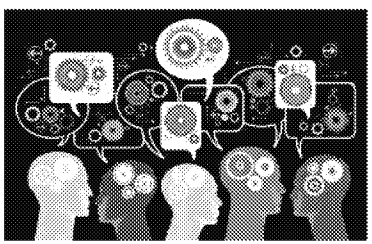
- Lecture (5%)
- Practice by doing (75%)
- Group discussion (50%)

Premise

- Focus is on decision-making

Level

- Introductory



Modules

- Environmental
- Chemical with 3 scenarios

Design

- Flexible for participation by groups with different backgrounds and perspectives
  - Students, as well as professionals in public and private sectors
- Generic and fundamental problem solving: Make a decision for a given situation

  Situation → Decision
  - Does not consider whose resources will be used or logistics
  - Not specific requirements of a particular regulatory scheme
  - Emphasize logic and reasoning and not specific tools
  - As much as possible, focus purely on "how to solve the problem"
- Reflect technical trends in risk assessment & needs: efficiently reaching decisions and communicate risks graphically

HESI RISK21 Publications

- Timothy P. Pastoor, Ammie N. Bachman, David R. Bell, Samuel M. Cohen, Michael Dellarco, Ian C. Dewhurst, John E. Doe, Nancy G. Doerrer, Michelle R. Embry, Ronald N. Hines, Angelo Moretto, Richard D. Phillips, J. Craig Rowlands, Jennifer Y. Tanir, Douglas C. Wolf, Alan R. Boobis, A 21st century roadmap for human health risk assessment. *Critical Reviews in Toxicology* Aug 2014, Vol. 44, No. S3: 1–5.
- Embry MR, Bachman AN, Bell DR, Boobis AR, Cohen SM, Dellarco M, Dewhurst IC, Doerrer NG, Hines R, Moretto A, Pastoor TP, Phillips R, Rowlands C, Tanir J, Wolf DC, Doe JE, Risk assessment in the 21st century: Roadmap and matrix, *Critical Reviews in Toxicology* Aug 2014, Vol. 44, No. S3: 6–16.
- Simon TW, Simons SS, Preston RJ, Boobis AR, Cohen SM, Doerrer NG, Fenner-Crisp PA, McMullin TS, McQueen CA, Rowlands CJ, The use of mode of action information in risk assessment: Quantitative key events/dose-response framework for modeling the dose-response for key events, *Critical Reviews in Toxicology*, 2014, 44(SUPPL3), pp. 17-43.
- Lin, Y.J. You SH, Chou WC, Weng CY,Chang HH, Chan WC, Lin WH, Chiang HC, Lin P, A RISK21 matrix for assessing the potential health risk of DDT from flower tea in Taiwan, *Taiwan Journal of Public Health*, 2016, 35(3), pp. 332-341.
- Wolf DC., Bachman A., Bachman A, Barrett G, **Bellin C**, Goodman JJ, Jensen E, Moretto A, McMullin T, Pastoor TP, Schoeny R, **Slezak B**, Wend K, Embry MR, Illustrative case using the RISK21 roadmap and matrix: Prioritization for evaluations of chemicals found in drinking water, *Critical Reviews in Tox*, 2016, 46(1), pp. 43-53.
- Doe JE, **Lander DR.,** Doerrer, NG, Heard N, Hines RN, Lowit AB, Pastoor TP, Phillips RD, Sargent, D, Sherman JH, Tanir JY, Embry MR,Use of the RISK21 roadmap and matrix: Human Health risk assessment of the use of a pyrethroid in bed netting, *Critical Reviews in Tox*, 2016, 46(1), pp. 54-73.
- Solomon KR, Wilks MF, Bachman A, Moretto A, Pastoor TP, Phillips R, Embry MR, Problem formulation for risk assessment of combined exposures to chemicals and other stressors in humans(Review), *Critical Reviews in Toxicology,2016,*46(10), pp 835-844 .
- Moretto A, Bachman A, Boobis A, Solomon KR, Pastoor TP, Wilks MF, Embry MR, A framework for cumulative risk assessment in the 21st century(Review), *Critical Reviews in Toxicology*, 2017 47(2), pp. 85-97.
- Dellarco M, Zaleski R, **Gaborek BJ**. Qian, H, **Bellin CA**, Egeghy, PS, **Lander DR**, Sunger N, Stylianou KS, Tanir JY, Using exposure bands for rapid decision making in RISK21 tiered exposure assessment, *Critical Reviews in Toxicology*, 2017 47(4), pp. 317-341.

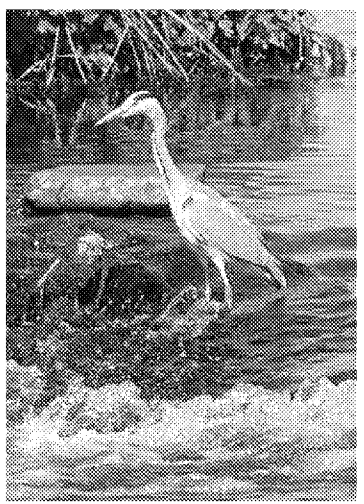
Human health and environmental risk assessment

- Formal process of estimating association between exposure to a stressor and the possibility of some adverse health outcome
- Stressor (agent) examples = chemical, biological, or physical
- Adverse health outcomes
  - Humans – cancer and non-cancer; safety
  - Environmental – compartments used as surrogate (i.e., air, water, soil) for entire populations or communities, usually not individuals
- Documented qualitatively or quantitatively

Risk assessment equation

Risk = function of Hazard and Exposure

- General population, workers and environmental populations



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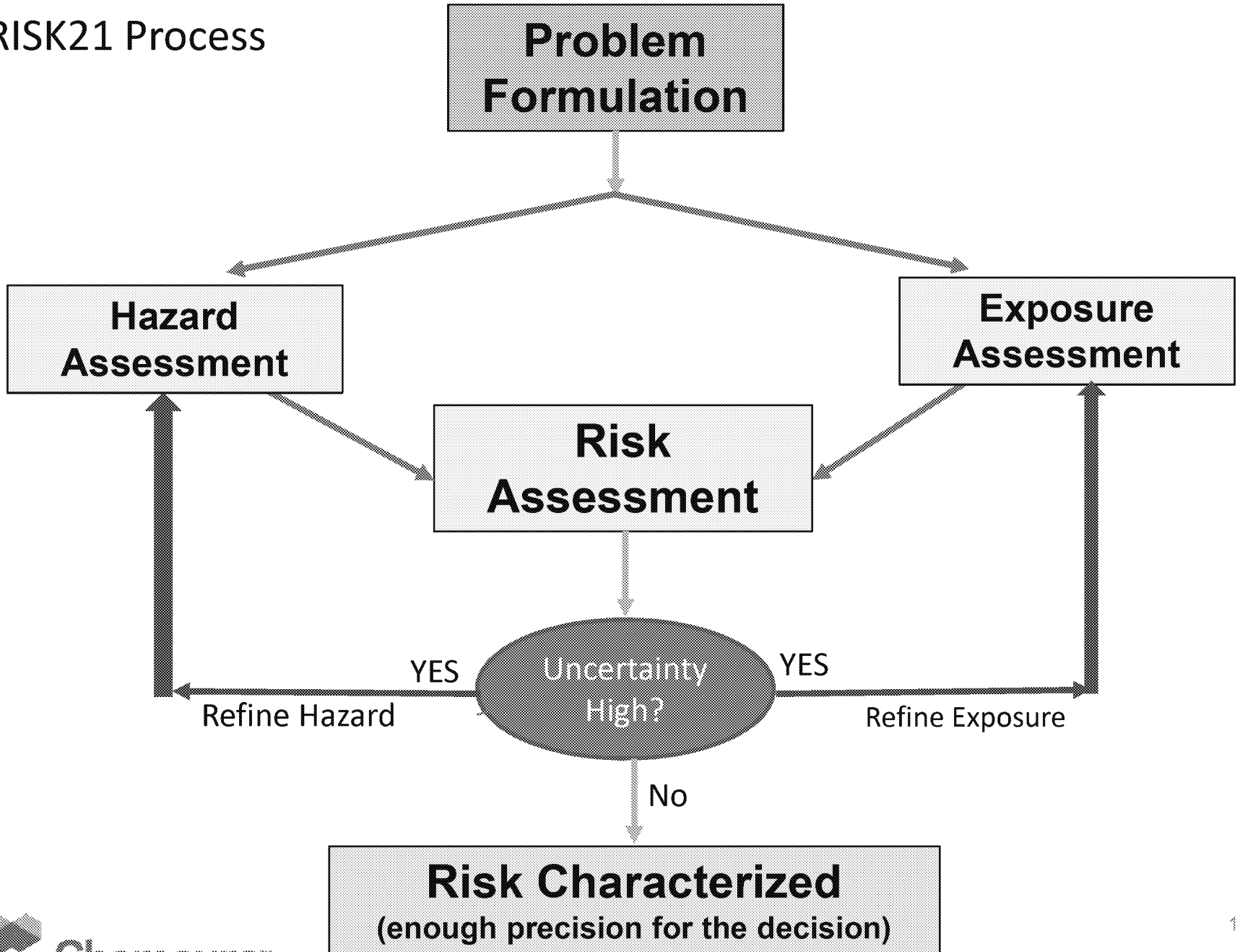
Risk Assessment in the 21st Century

- Considerable research has been published on advancing Risk Assessment in the 21st Century (references at end)
- Science and Decisions: Advancing Risk Assessment
  - U.S. National Academy of Sciences, 2009
  - Problem formulation as a key element
  - Download for free at: https://www.nap.edu/catalog/12209/science-and-decisions-advancing-risk-assessment
- RISK21
  - "…a problem formulation-based, exposure-driven, tiered acquisition approach that leads to an informed decision."
  - Project led by Health and Environmental Sciences Institute (HESI)
    - Non-profit scientific organization since 1989
    - Collaborative approaches to drug and chemical safety, risk assessment, and innovation
    - **Mission:** Engage scientists from academia, government and industry to identify and resolve global health and environmental issues.
    - http://www.risk21.org/ & www.hesiglobal.org
- Integrated Approaches to Testing and Assessment (IATA)
  - "IATA are pragmatic, science-based approaches for chemical hazard characterization that rely on an integrated analysis of existing information coupled with the generation of new information using testing strategies."
  - OECD
  - http://www.oecd.org/chemicalsafety/risk-assessment/iata-integrated-approaches-to-testing-and-assessment.htm
- RISK21 approach will be used today for RiskChallenge

How is RISK21 Different?

- Think about the problem that needs to be addressed; then select sources of information which will have the most value
- RISK21 Principles:
  - Problem-formulation based
  - Equal focus on Exposure and Hazard
  - Prior knowledge
  - "Enough precision to make the decision"
- Provide a framework that is…
  - Flexible
  - Transparent
  - Visual

RISK21 Process



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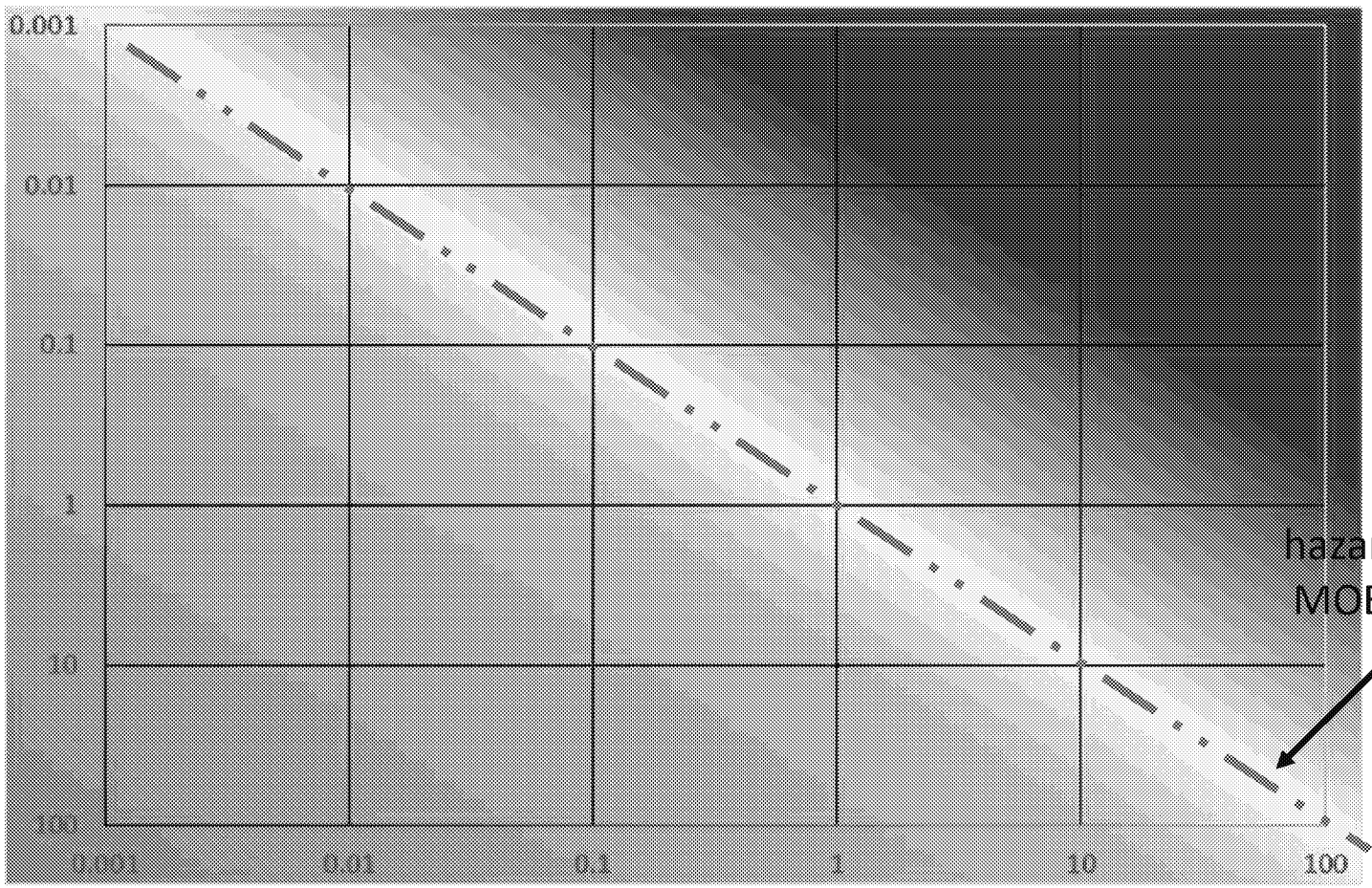
RISK21 PLOT

log/log scale



Estimate of Toxicity (mg/kg/day or mg/L)

hazard/exposure,
MOE = 1

Estimate of Exposure (mg/kg/day or mg/L)

Used with permission from HESI RISK21 project

Problem formulation

- Identification of what information is already known
- Decisions about what:
  - Work needs to be completed
  - Technical approach to take
  - Level of effort is required for decision-making
- Desired outcome is a written and visual conceptual model linking:
  - Stressor(s)
  - Exposed population(s)
  - Endpoint(s)

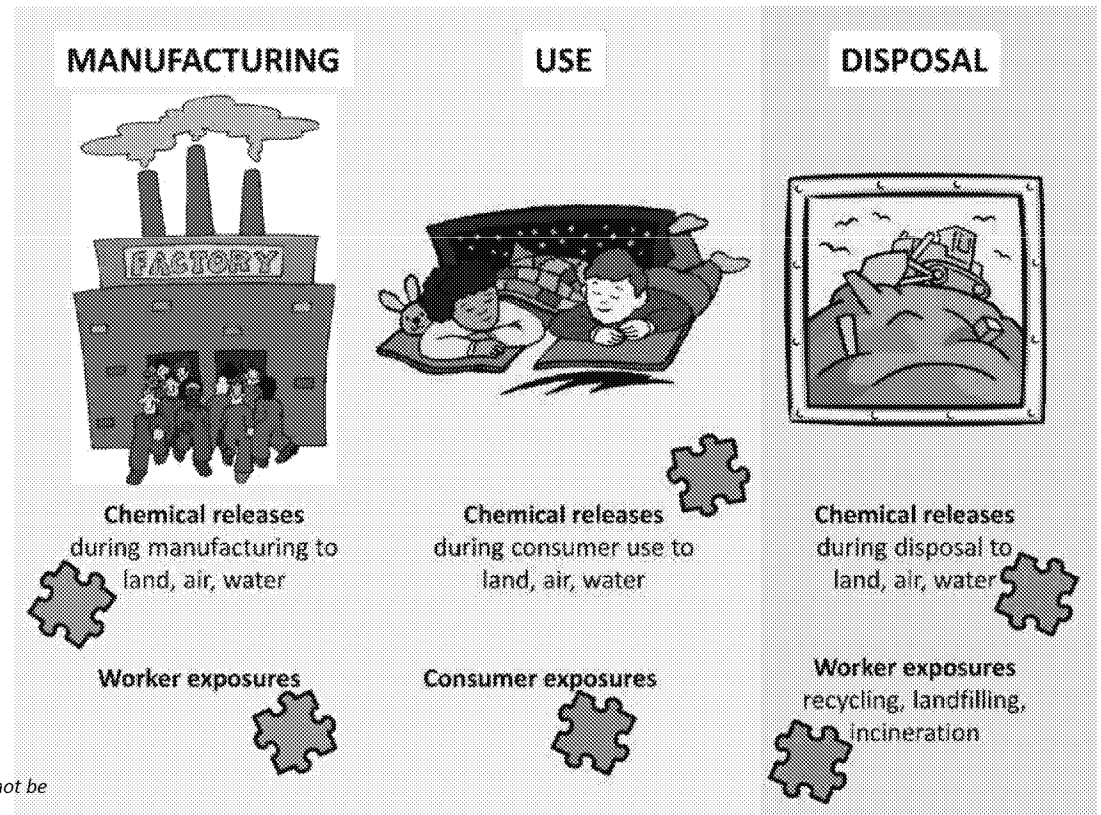
Exposure assessment definitions

- Exposure – Contact over a given exposure period between a stressor and a human or ecological receptor
  - Stressor (agent) – Induces an adverse response in the receptor
  - Receptor – Population, subpopulation, organism, organ, tissue, or cell
  - Exposure period – Time of continuous contact between a stressor and a receptor

- Exposure Pathways:

Follow the Life Cycle:

- Exposure route
  - Inhalation (Breathing)
  - Dermal (Skin contact)
  - Ingestion (Eating and drinking)

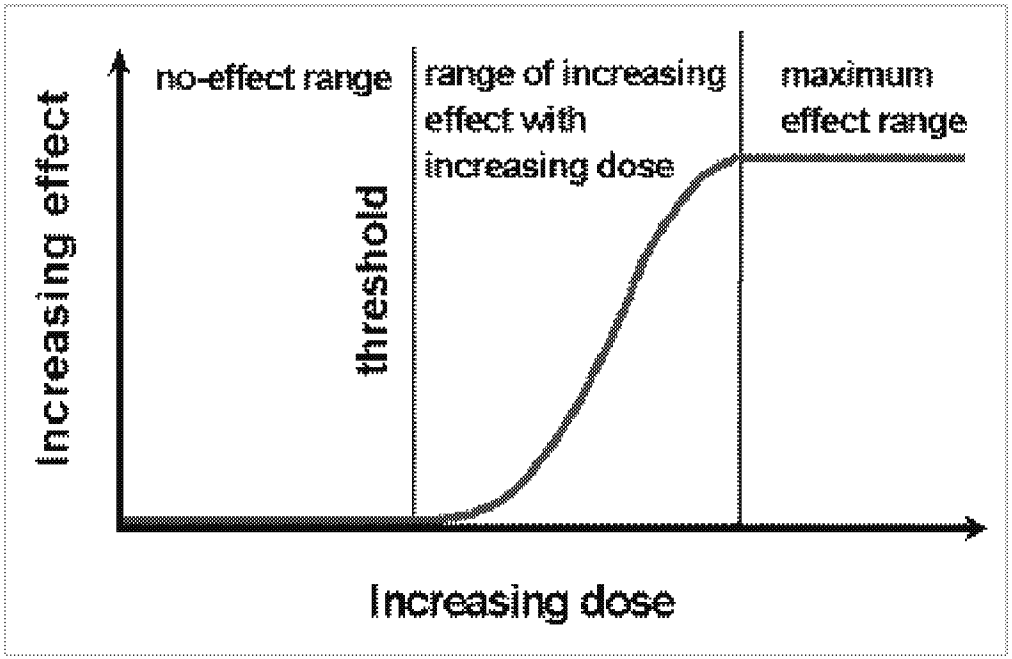


Early Use of Exposure

- Exposure estimates can guide the amount and type of toxicity data necessary for the risk assessment.
- Exposure estimates can be used to prioritize chemicals for further exposure and toxicity testing.
- If the exposure estimate is very low, then it may be adequate to utilize a lower-precision, lower-tier approach for toxicity estimation.

Human Health Hazard Assessment

- Purpose of assessment is to determine how much exposure will cause what effect
- Incorporate “safety factors” into the calculation to get benchmarks
- Non-cancer effects generally are considered to have a threshold



Environmental hazard assessment

- Purpose of assessment is to determine concentrations in the compartment that will cause no effect to the relevant environmental species
- Typical environmental compartments:
  - Surface water (freshwater or marine water)
  - Sediments
  - Soil
  - Air

- Studies are performed on the relevant environmental species
- Ecotoxicologists review the available studies to estimate the Predicted No Effect Concentration in each compartment using assessment factors
- When only aquatic testing is available the partition equilibrium method is used to estimate sediment and soil values based on Koc and the aquatic predicted no effect concentration.

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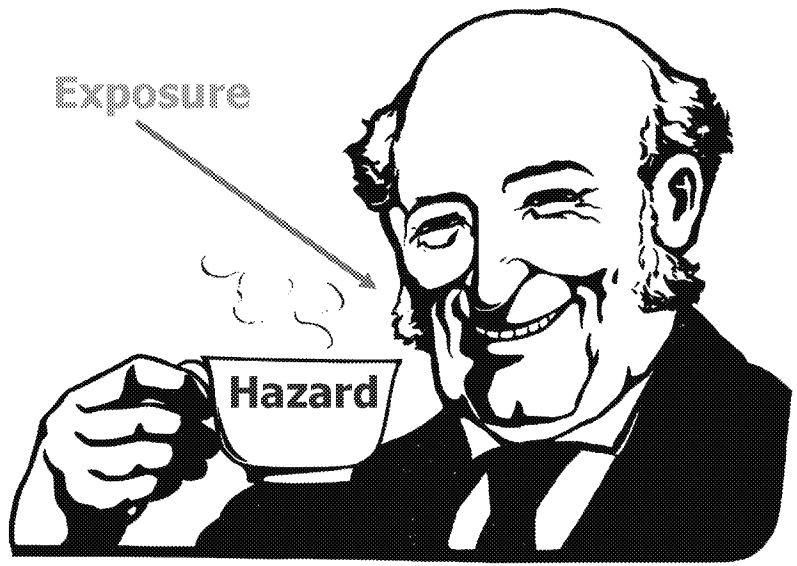
Risk characterization

Risk characterization combines the information obtained on hazard with the estimated exposure to provide an estimate of risk



Risk characterization…..

- Provides a numerical estimate of risk
- Includes identifying key uncertainties (experimental error, variability of biological systems, extrapolation)
- Compares numerical estimate of risk with a previously determined risk goal
- Non-cancer risk (hazard) and environmental risk:
  - Hazard Quotient (HQ), Risk Characterization Ratio (RCR), or Margin of Exposure (MOE)
    - HQ or RCR = $\frac{Exposure}{Benchmark}$ < 1
    - MOE = $\frac{Benchmark}{Exposure}$ > 1

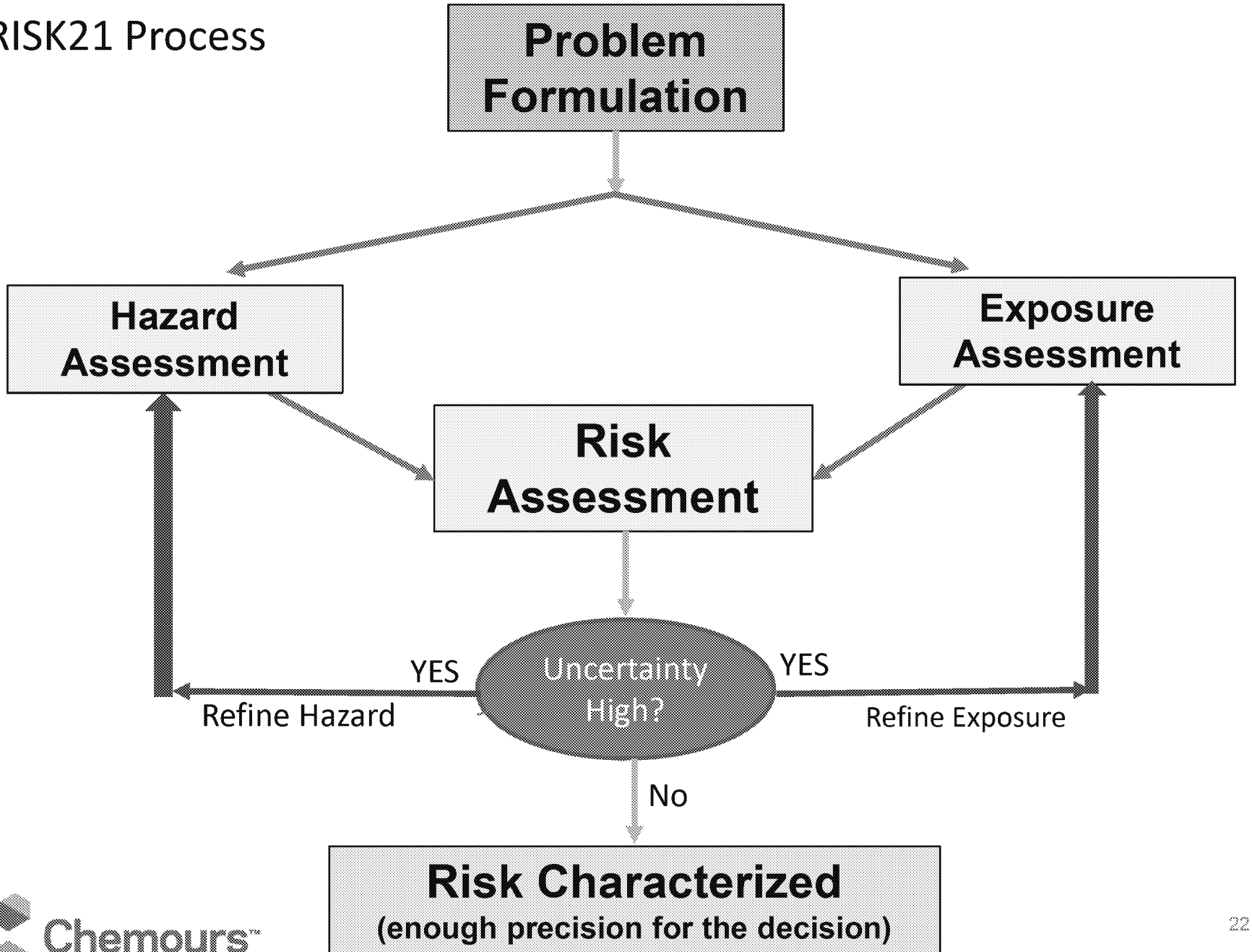
Risk Characterization

- Quantitative and/or qualitative integration of toxicity and exposure assessment results
- Proper interpretation, documentation and presentation of the result are key for effective communication of results
- Risk results should be properly qualified
  - Do not attribute great precision to risk numbers
  - Evaluate uncertainties qualitatively or quantitatively

Key messages regarding risk assessment

- Helps **answer a wide variety of health and safety questions**
- Key components include the **hazard and exposure assessments**
- Often **iterations** are necessary
- **More detailed** inputs ensure **more certain results and conclusions**
- **Conclusions** used to help make **risk management decisions**

RISK21 Process



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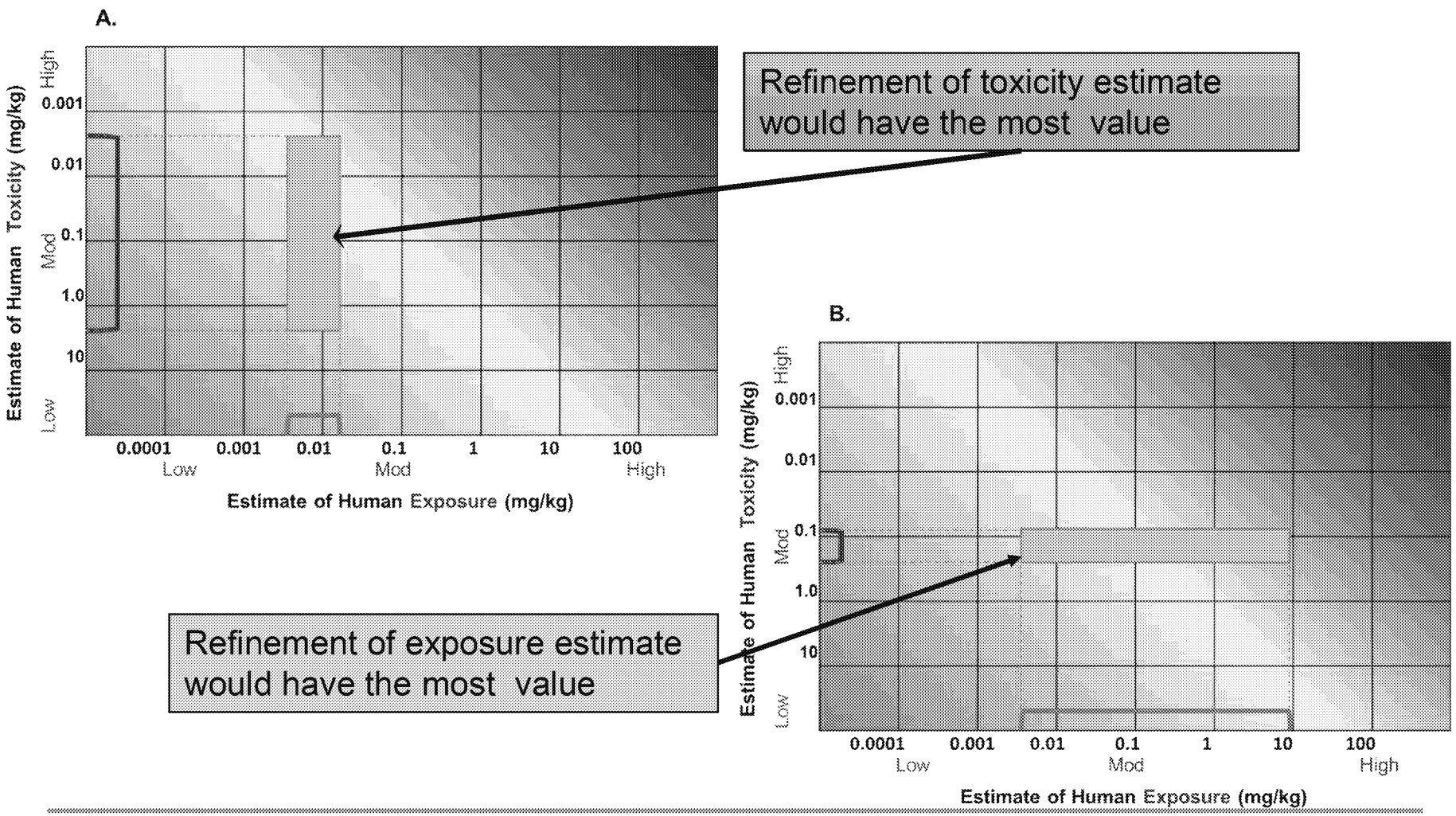
Using the RISK21 Plot for Targeted Refinement



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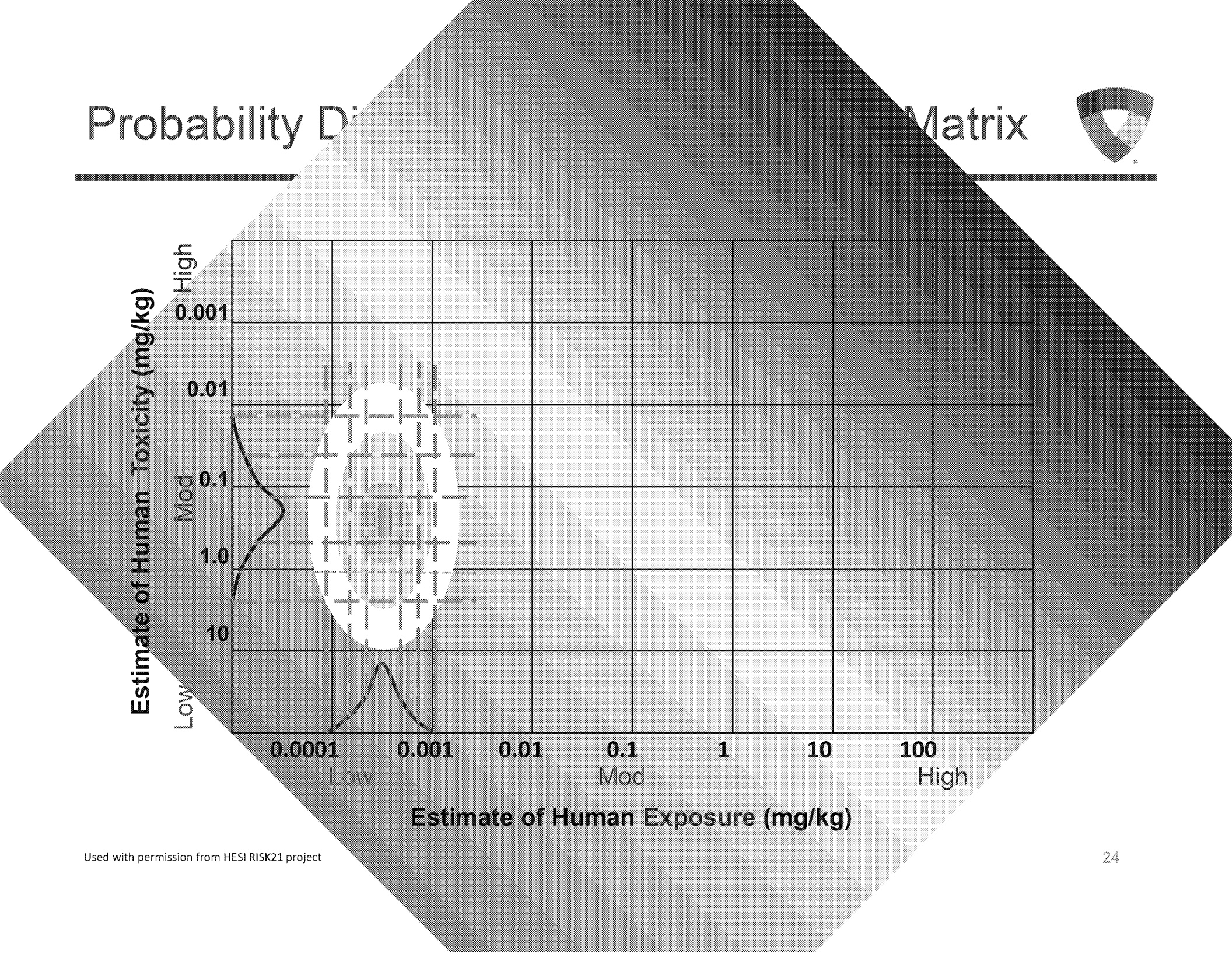
Probability Di Matrix



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So how do you play RiskChallenge?

After problem formulation the data must be collected to characterize hazard and exposure

1) Phys Chem and Environmental Fate

Study #	Tasks	Estimated cost (USD)	OECD TG or other	Time forecast (months)	Prerequisite (study or QSAR)
	PHYS.-CHEM.				
1	Basic Phys-Chem tests (Mp, Bp, Vp, Density, Water Solubility, Log Kow)	$27,000	102, 103 109, 104 105, 117	3	
2	Phys-chem QSARs (Mp, Bp, Vp, Water Solubility, Log Kow)	$1,000	Model	0.5	
	ENVIRONMENTAL FATE				
3	Ready biodegradability	$4,000	301	3	
4	Fate/Behaviour - Adsorption/desorption screening study (Koc)	$11,000	106	3	
5	EFATE QSARs (ready biodegradability, Koc)	$1,000	Model	0.5	phys chem

- These tests inform on how the chemical behaves in the environment
- This helps identify exposure potential (for humans and environment)

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Environmental Toxicity

- Will the substance have effects on species that live in soil, water, and sediment?
- There are many tests that can be performed and this list is a reduced set for simplicity

Study #	Tasks	Estimated cost (USD)	OECD TG or other	Time forecast (months)	Prerequisite (study or QSAR)
	ECO-TOXICITY				
6	Short-term aquatic toxicity testing on 3 species (crustacea, algae, fish), the resulting Predicted No Effect Concentrations are also included	$45,000	202, 201, 203	6	
7	Long-term aquatic toxicity testing on 2 species (crustacea, fish) , the resulting Predicted No Effect Concentrations are also included	$120,000	210, 211	6	
8	Activated sludge respiration inhibition testing (sewage treatment plants), the resulting Predicted No Effect Concentration is also included	$5,000	209	3	
9	Ecotox QSAR for short-term toxicity testing on 3 species	$3,000	Model	0.5	phys chem and Koc

- Predicted no effect levels are estimated and included in data

Once the Exposure Paths are Identified

- Time to perform modeling or monitor for exposure

Study #	Tasks	Estimated cost (USD)	OECD TG or other	Time forecast (months)	Prerequisite (study or QSAR)
	EXPOSURE INFORMATION				
10	Industrial Worker Formulation Use Exposure Assessment (modeling)	$3,000	Model	1	phys chem
11	Professional Spray Painting Use Exposure Assessment (modeling)	$3,000	Model	1	phys chem
12	Consumer Spray Painting Exposure Assessment (modeling)	$3,000	Model	1	phys chem
13	Environmental Risk Assessment includes all uses (modeling)	$10,000	Model	1	phys chem and EFATE
14	Worker Formulation Use Exposure monitoring data	$25,000	Data	6	
15	Professional Spray Painting Use Monitoring Data	$50,000	Data	12	
16	Consumer Spray Painting Exposure monitoring data	$150,000	Data	24	
17	Environmental Water concentration Monitoring Data	$300,000	Data	24	

- Modeling is conservative and gives estimates to help identify where toxicity testing is most beneficial

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Mammalian Toxicity (short term studies)

- Will need to assess the hazards of the new chemical

SELECT	Study #	Tasks	Estimated cost (USD)	OECD TG or other	Time forecast (months)	Prerequisite (study or QSAR)
		MAMMALIAN TOXICITY				
	18	Standard Suite of 3 in-vitro tests for local effects (skin irritation, eye irritation, skin sensitisation)	$18,000	435 437 442	3	
	19	Standard Suite of 3 in-vitro tests for mutagenicity and cytogenicity	$80,000	471 473 476	6	
	20	Acute toxicity, oral route (determine lethal dose based on 4 hrs exposure)	$5,000	420	3	
	21	Acute toxicity, inhalation (determine lethal dose based on 4 hrs exposure)	$25,000	403	3	
	22	Acute toxicity, dermal route, (determine lethal dose based on 4 hrs exposure)	$5,000	402	3	

- Local effects must be evaluated (irritation, sensitization)
- Must check for mutagenicity (cancer)
- Acute toxicity by most relevant route must be investigated (helps to determine dosing range for higher tier studies)

Mammalian Studies (longer-term studies)

Need repeat dose testing to provide quantitative information on dose response

Study #	Tasks	Estimated cost (USD)	OECD TG or other	Time forecast (months)	Prerequisite (study or QSAR)
	Mammalian Toxicity				
23	Short-term combined repeated dose toxicity study - 28 days, oral route (with repro and development screening)	$250,000	422	12	acute toxicity, in-vitro local effects
24	Short-term repeated dose toxicity study - 28 days, oral route	$120,000	407	10	acute toxicity, in vitro local effects
25	Short-term repeated dose toxicity study - 28 days, inhalation route	$165,000	412	10	acute toxicity, in vitro local effects
26	Short-term repeated dose toxicity study - 28 days, dermal route	$140,000	410	10	acute toxicity, in vitro local effects
27	Sub-chronic toxicity study - 90-day oral route	$200,000	408	11	28 day
28	Pre-natal developmental toxicity study, oral route	$100,000	414	10	28 day
29	Pre-natal developmental toxicity study, inhalation route	$200,000	414	10	28 day
30	Two-generation reproduction toxicity study, oral route	$600,000	416	16	28 or 90 day
31	Combined Chronic toxicity and Carcinogenicity study (2 yrs), oral route	$1,700,000	453	36	28 or 90 day
32	Mammalian Genotoxicity and Carcinogenicity QSAR and Estimate of chronic toxicity based on Threshold of Toxicological Concern (TTC) approach	$3,000	Model	0.5	phys chem

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The Difficult Translation of Hazard from Animal to Human

- Ideal mammalian studies will dose at a level that shows adverse effects and a level that does not. The no observed adverse effects level in animals is then converted into a human derived no effect level.
- Application of Safety Assessment (or Uncertainty) factors can be used to estimate human derived no effect level
- There are many approaches, Table below describes Uncertainty Factors used for RiskChallenge which are loosely based on EU ECHA Guidance R8 Characterization of dose-response for human health

Toxicity Test	Duration Extrapolation	Interspecies	Intraspecies	Quality of Database	Total Assessment Factor
28 day	6	10	5 for worker 10 for consumer	2	600 1200
90 day	2	10	5 for worker 10 for consumer	1	100 200
1 yr or longer	1	10	5 for worker 10 for consumer	1	50 100
Human Data	1	1	5 for worker 10 for consumer	1	5 10

For exercise today, "Total Assessment Factor" (highlighted) is used for plotting uncertainty

How about a demonstration?

Let’s go through an simplified example that everyone can understand

Example: Are humans exposed to too much caffeine?

- Step one: Problem Formulation
- What are properties of caffeine (phys-chem, efate)?

Study #	Tasks	Estimated cost (USD)	OECD TG or other	Time forecast (months)	Prerequisite (study or QSAR)
	PHYS.-CHEM.				
1	Basic Phys-Chem tests (Mp, Bp, Vp, Density, Water Solubility, Log Kow)	$27,000	102, 103 109, 104 105, 117	3	
2	Phys-chem QSARs (Mp, Bp, Vp, Water Solubility, Log Kow)	$1,000	Model	0.5	
	ENVIRONMENTAL FATE				
3	Ready biodegradability	$4,000	301	3	
4	Fate/Behaviour - Adsorption/desorption screening study (Koc)	$11,000	106	3	
5	EFATE QSARs (ready biodegradability, Koc)	$1,000	Model	0.5	phys chem

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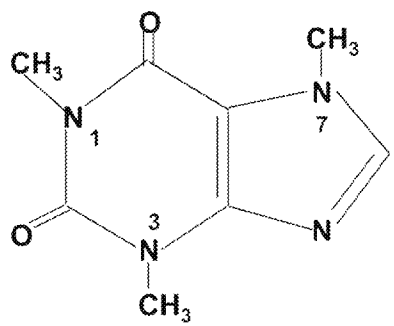
Example: Are humans exposed to too much caffeine?

- What are the routes of exposure?

	Industrial		Consumer	
	Hazard	Exposure	Hazard	Exposure
Oral				
Dermal				
Inhalation				
Environmental (human)				
Environmental (water, air, soil)				

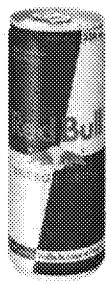


Problem Formulation Refined: Can consumers drink too much caffeine in a day?

- Exposure Assessment: identified Coffee, Black tea, Energy Drinks (Red Bull), Coca-Cola, as significant sources of caffeine.

90 mg/8oz

80 mg/8oz



80 mg/8oz

60 mg/12oz

- Hazard Assessment: Unique case where epidemiological data exist.

The safe daily dose of this chemical is:
- Not recommended for children under 12
- Acute toxicity is seen at doses > 3 mg/kg body weight/day
- Once in the body it takes about 4 hrs for half of it to disappear

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Hazard Data Card

Study: Human Epidemiology Study

Time Required: 12 months

Results	OECD TG or other	Additional Information
ACUTE NOAEL = 3 mg/kg bw/day Effect: nervousness, fast heartbeat, insomnia		Based on Human epidemiology data

Interpretation
The No observed adverse effect level (NOAEL) in animals can be divided by the appropriate assessment factor to obtain the No effect level in humans for the oral route of exposure. Since this is a human study, the uncertainty factor is 10 and only general population was considered or oral route exposure to caffeine **Values used for Hazard Axis of RISK21 PLOT for consumers** range of 0.3 mg/kg/day – 3 mg/kg/day

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Exposure Data Card

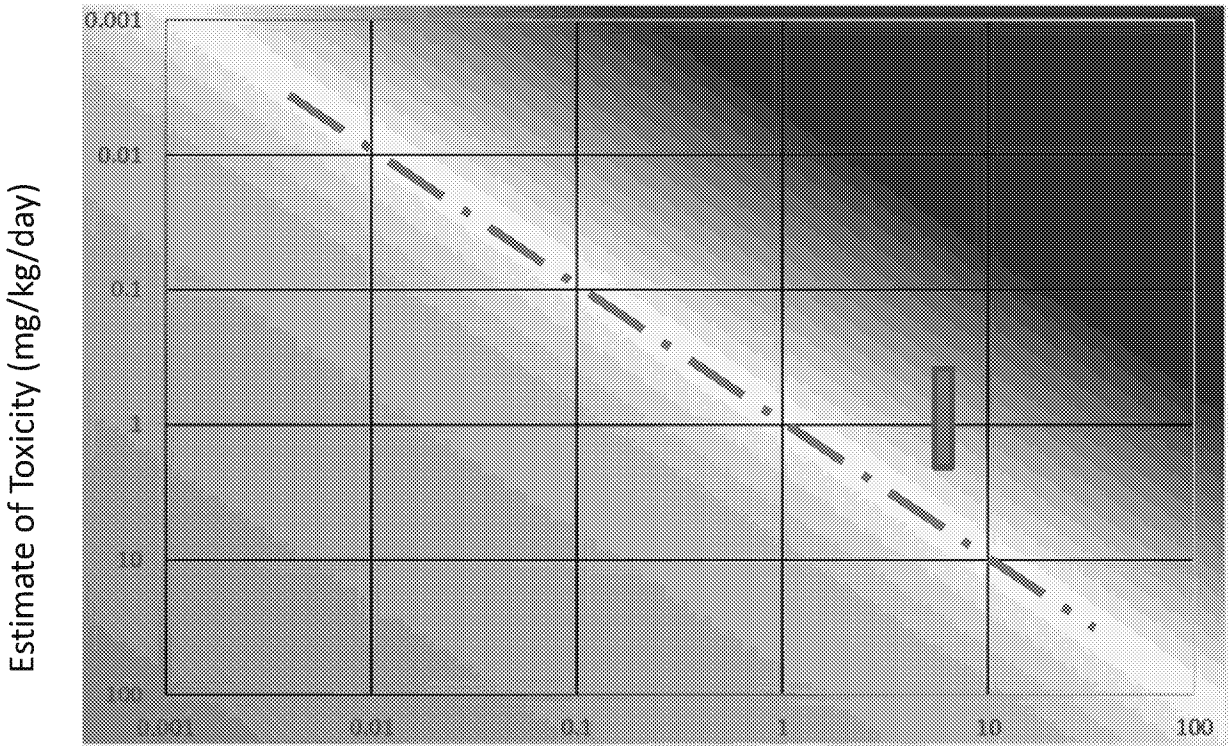
Study: Consumer Exposure Calculation

Time Required: 1 day

Results	OECD TG or other	Additional Information
16 yr, 60 kg young man drinks and a mountain dew (60 mg), a double latte (140 mg), and an energy drink (80 mg) in 2 hrs. The caffeine ingested = 60+140+80 = 280 mg Exposure = 280 mg/60 kg = 5 mg/kg/day	Calculation	

RISK21 PLOT for Caffeine Ingestion Scenario

- Acute Effects are expected
- Warning signs of toxic doses of caffeine include anxiety, sweat, increased blood pressure, heart palpitations, headaches and generally feelings of nervousness.
- The dose was consumed in such a short time (<<24hrs) resulting in a magnification of effects



RISK21 Approach Summary

A transparent framework for knowledge synthesis to enable effective decision-making:

- Problem formulation-based: An iterative process that establishes purpose, scope, and a plan for collecting and evaluating information
- Utilizes existing information: Applies information on inherent chemical properties as well as existing exposure and toxicity information before generating additional data
- Exposure-led: Considers relevant exposure estimates up-front to prioritize and determine data needs
- Tiered: Optimizes use of resources
- Flexible: Allows one to make an informed decision on human health safety as soon as sufficient

"Enough precision to make the decision"

Used with permission from HESI RISK21 project

Time to Start RiskChallenge

- A substance can be added to latex paint at 1% to significantly improve the lifetime of the coating, which is environmentally beneficial by reducing paint use.
- Are there any risks to humans or environment from the manufacture, use and disposal of this new substance at 800 tonnes/yr?
- It is a clear viscous liquid at room temperature and standard atmospheric pressure.
- It is not volatile and has no ionizable functional groups.
- The substance is stable and no relevant degradation products are formed.
- The scope will be limited to 4 scenarios:
  - Industrial use: workers formulation and repackaging
  - Professional use: Use of latex paints with pneumatic spraying
  - Consumer use: Use of latex paints (spray uses included)
  - Environmental impact from uses (environmental compartments and human via the environment)

Group into Work Teams for 2 hr exercise

- Each team will be given a supply of money and a time limit to come to a decision
- Start with problem formulation (<30 minutes)
- Select multiple data to purchase from menu, bring it to us and we will tabulate your costs and time consumed on the computer and give you the data.
- Buy data in rounds, the longest test time selected per round will counted toward time limit
- Evaluate data, Make Risk21 Plot, refine hazard or exposure by purchasing more data
- Make Final Risk21 Plot and come to a decision (<30 minutes)

Debrief session team report

- Identify Margin of Exposure (MOE) on a RISK21 risk plot
- Identify uncertainty on a RISK21 risk plot
- Summarize team decision, identifying
  - Any concerns
  - Any risk management measures
- Comment on what the team feels were the most useful data and why
- To help us improve, impressions and suggestions about workshop would be much appreciated

RiskChallenge

Debrief

Example 1: Some resource constraints

Information	Cost (USD)	Time (months)	Group
Basic Phys-Chem tests	$27,000	3	I
EFATE QSARs	$1,000	0.5	I
Standard Suite of 3 in-vitro tests for local effects (skin irritation, eye irritation, skin sensitisation)	$18,000	3	I
Standard Suite of 3 in-vitro tests for mutagenicity and cytogenicity	$80,000	6	II
Short-term aquatic toxicity testing on 3 species (crustacea, algae, fish), the resulting Predicted No Effect Concentrations are also included	$45,000	6	II
Activated sludge respiration inhibition testing (sewage treatment plants)	$5,000	3	II
Acute toxicity, oral route (determine lethal dose based on 4 hrs exposure)	$5,000	3	II
Industrial Worker Formulation Use Exposure Assessment (modeling)	$3,000	1	II
Professional Spray Painting Use Exposure Assessment (modeling)	$3,000	1	II
Consumer Spray Painting Exposure Assessment (modeling)	$3,000	1	II
Environmental Risk Assessment includes all uses (modeling)	$10,000	1	II
Short-term combined repeated dose toxicity study - 28 days, oral route (with repro and development screening)	$250,000	12	II
	$450,000	21	

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Example 1: Risk Assessment Rationale

RESULTS	Hazard	Exposure (dermal + inhalation)	Decision
Industrial Workers	0.3 -200 mg/kg/day	0.8-5.0 mg/kg/day	Needs more refinement
Professional Workers	0.3 -200 mg/kg/day	1.2-6.7 mg/kg/day	Need more refinement
Consumers	0.2 -200 mg/kg/day	0.06 -0.6 mg/kg/day oral exposure not assessed as not prime route of exposure (child eating paint = 0.02 mg/kg/day)	Minimal Concern
Environmental (human)	0.2-200 mg/kg/day	5E-06 - 2E-05 mg/kg/day	No Concern
Environmental (water, air, soil)	PNEC water > 10 mg/L PNEC STP = 200 mg/L	water = 0.05-0.65 mg/L STP = 0.05-0.65 mg/L	No Concern

Let's make a RISK21 PLOT

RISK21 PLOT

Combined Dermal and Inhalation Risk21 Plot for Example 1 (~2 yrs, $450K)

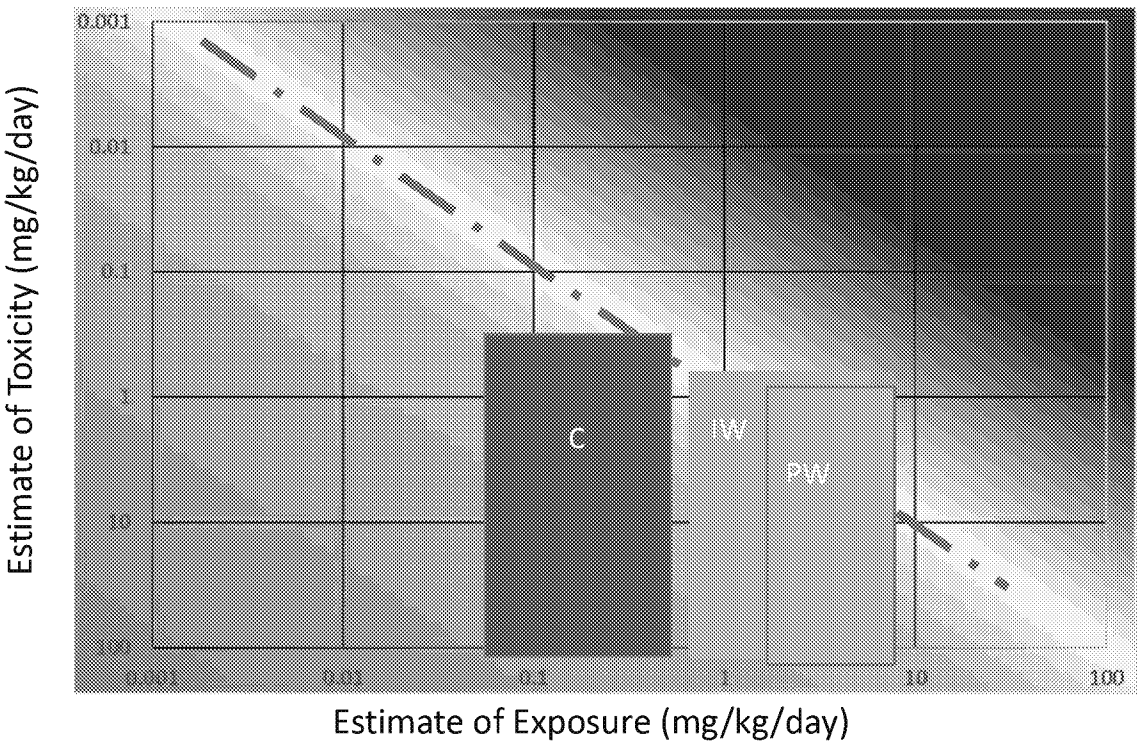
Hazard:
Based on oral 28 day toxicity test
(0.2-200 mg/kg/day)

Exposure:
Based on modeling

Needs refinement

Could either do longer term tox test to reduce uncertainty or refine exposure to reduce uncertainty

Worker risk could be mitigated with PPE, typically assume consumers do not wear PPE



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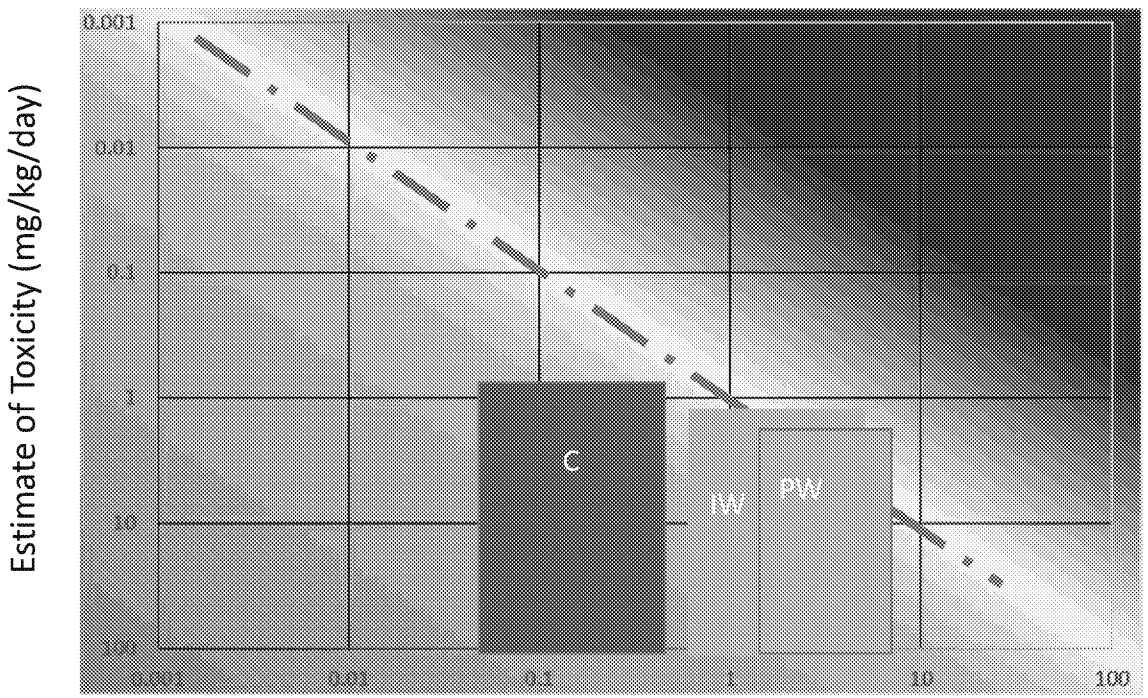
RISK21 PLOT

Combined Dermal and Inhalation Risk21 Plot for Example 1 + oral 90 day test (~3 yrs, $650K)

Hazard:
Based on oral 90 day toxicity test (0.75-1.5 mg/kg/day)

Exposure:
Based on modeling

Some refinement needed
Could require workers to wear gloves and have additional ventilation requirements or respiratory protection. This reduces exposure by 10X.

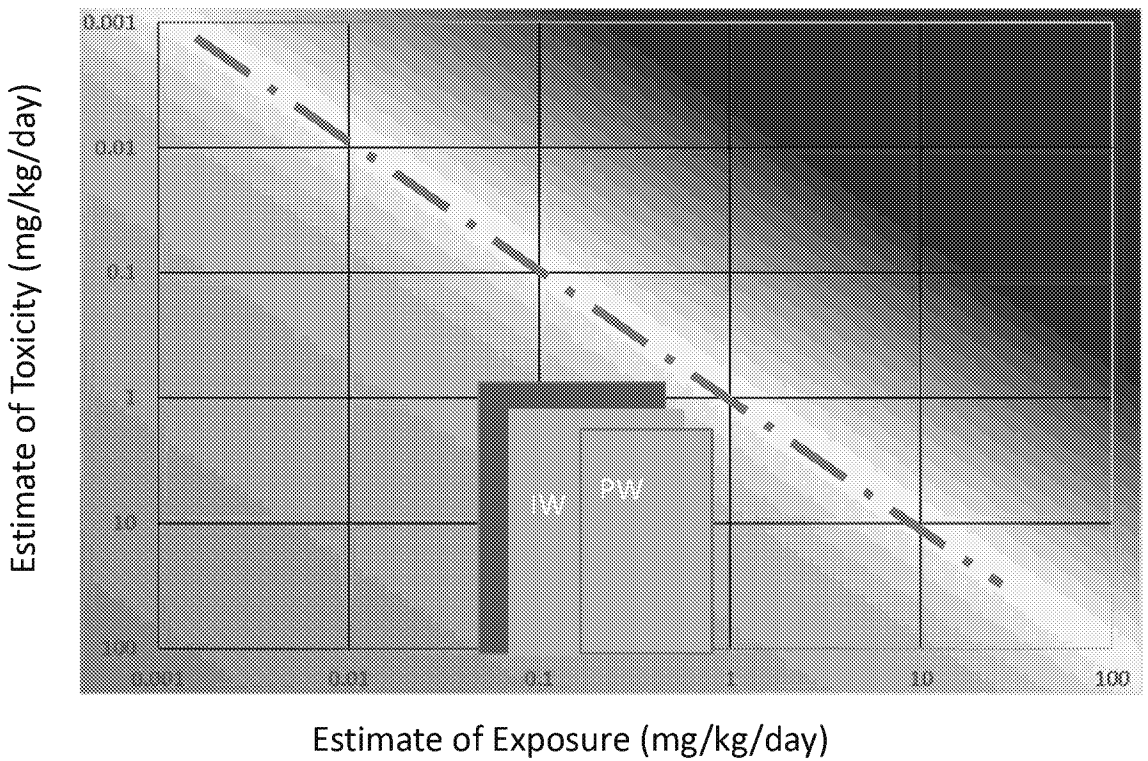


RISK21 PLOT

Combined Dermal and Inhalation Risk21 Plot for Example 1 + oral 90 day test (~3 yrs, $650K) with gloves and additional ventilation requirements for industrial and professional workers

Hazard:
Based on oral 90 day toxicity test (0.75-1.5 mg/kg/day)

Exposure:
Based on modeling



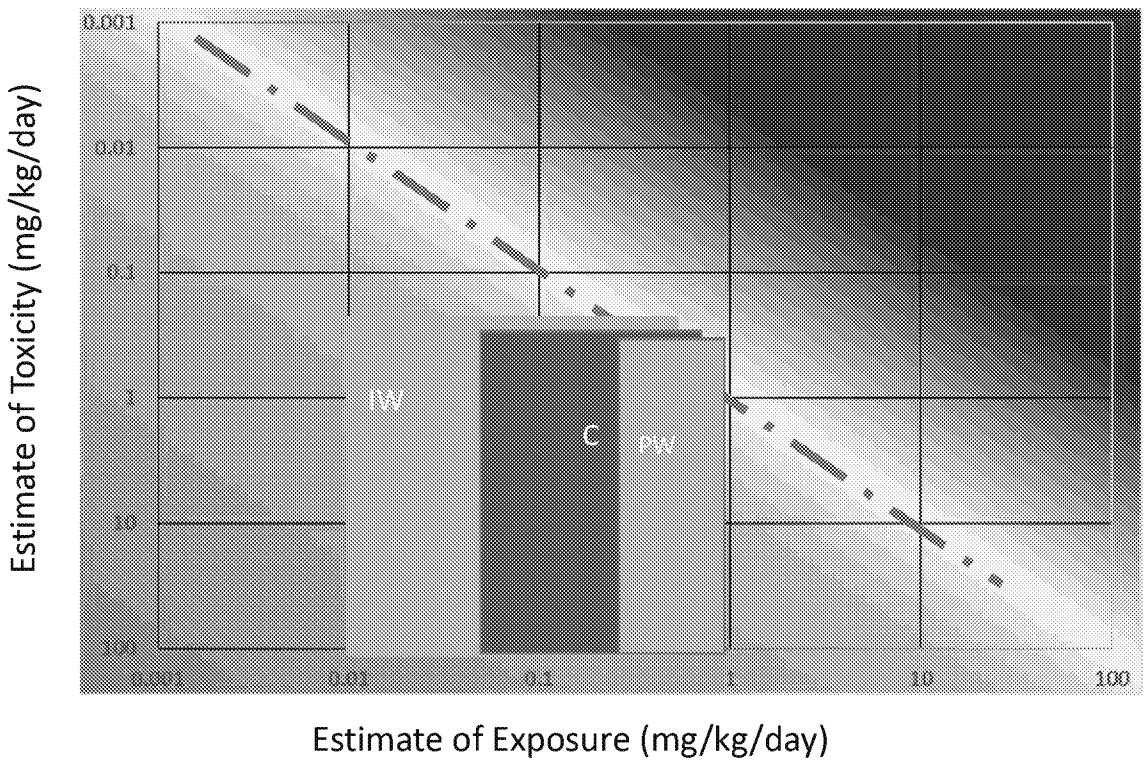
RISK21 PLOT

Combined Dermal and Inhalation Risk21 Plot for Example 1 added worker monitoring data (3 yrs, $525K)

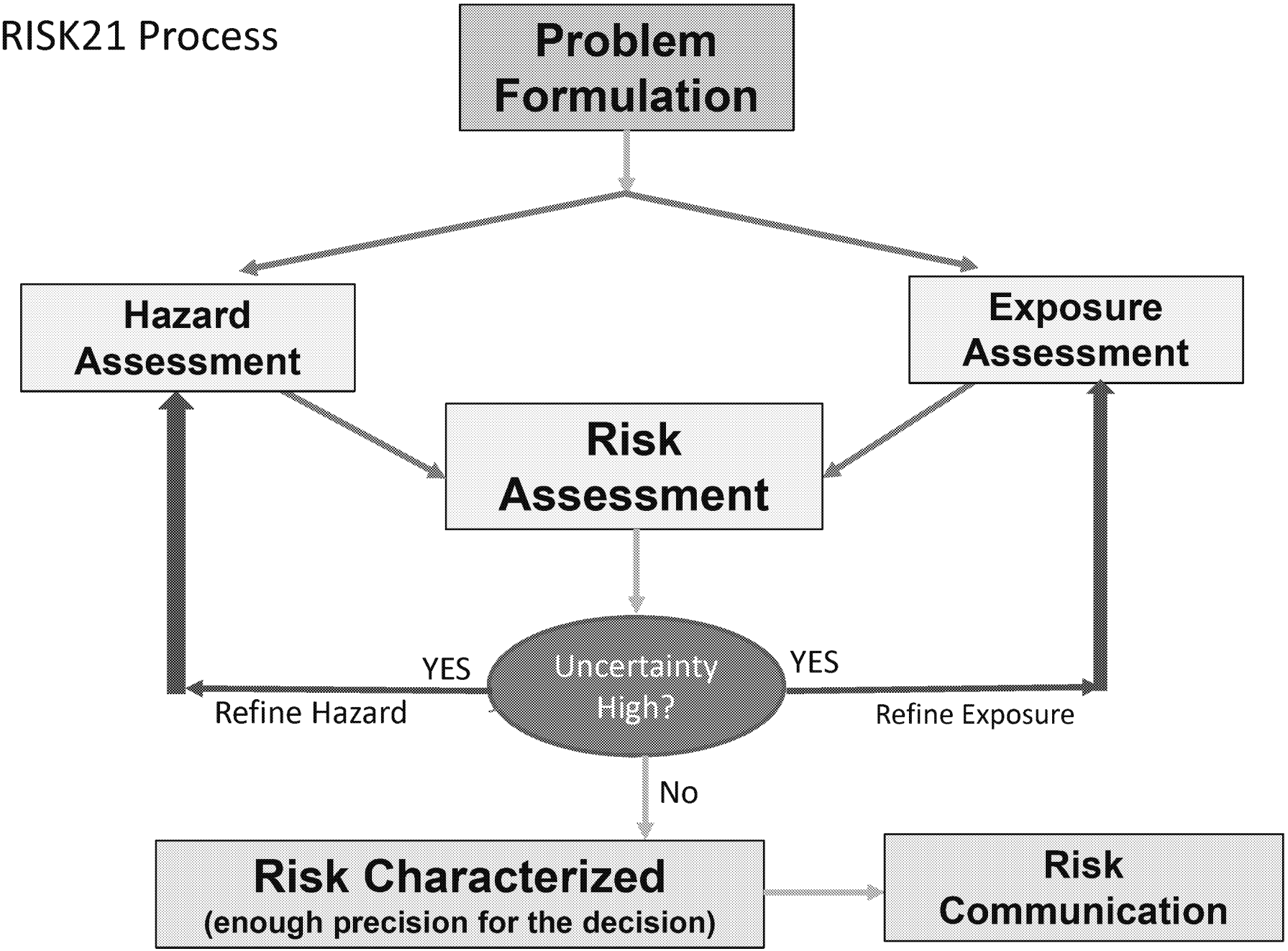
Hazard:
Based on oral 28 day toxicity test (0.2-200 mg/kg/day)

Exposure:
Based on modeling for consumers and monitoring data for workers

Just a little refinement needed
Since dermal exposure is significant can obtain in-vitro skin permeation data to show dermal absorption is much less than oral absorption (<10%).



RISK21 Process



This is a fictional scenario created for training purpose only and should not be interpreted or used as scientific data or information for other purposes

Example 2: No constraints on time or money

Information	Cost (USD)	Time (months)	Group
Basic Phys-Chem tests	$27,000	3	I
Fate/Behaviour - Adsorption/desorption screening study (Koc)	$11,000	3	II
Ready biodegradability	$4,000	3	II
Standard Suite of 3 in-vitro tests for local effects (skin irritation, eye irritation, skin sensitisation)	$18,000	3	II
Standard Suite of 3 in-vitro tests for mutagenicity and cytogenicity	$80,000	6	II
Acute toxicity, oral route (determine lethal dose based on 4 hrs exposure)	$5,000	3	II
Acute toxicity, inhalation (determine lethal dose based on 4 hrs exposure)	$25,000	3	II
Acute toxicity, dermal route, (determine lethal dose based on 4 hrs exposure)	$5,000	3	II
Activated sludge respiration inhibition testing (sewage treatment plants)	$5,000	3	II
Short-term aquatic toxicity testing on 3 species (crustacea, algae, fish), the resulting Predicted No Effect Concentrations are also included	$45,000	6	II
Short-term repeated dose toxicity study - 28 days, oral route	$120,000	10	III
Short-term repeated dose toxicity study - 28 days, inhalation route	$165,000	10	III
Short-term repeated dose toxicity study - 28 days, dermal route	$140,000	10	III
Long-term aquatic toxicity testing on 2 species (crustacea, fish)	$120,000	6	III
Industrial Worker Formulation Use Exposure Assessment (modeling)	$3,000	1	III
Professional Spray Painting Use Exposure Assessment (modeling)	$3,000	1	III
Consumer Spray Painting Exposure Assessment (modeling)	$3,000	1	III
Environmental Risk Assessment includes all uses (modeling)	$10,000	1	III
Worker Formulation Use Exposure monitoring data	$25,000	6	IV
Professional Spray Painting Use Monitoring Data	$50,000	24	IV
Pre-natal developmental toxicity study, oral route	$100,000	10	IV
Sub-chronic toxicity study - 90-day oral route	$200,000	11	IV
Two-generation reproduction toxicity study, oral route	$600,000	16	IV
Combined Chronic toxicity and Carcinogenicity study (2 yrs), oral route	$1,700,000	36	IV
Group II	$3,464,000	56	

Example 2 Risk Assessment Rationale

RESULTS	Hazard	Exposure (dermal + inhalation)	Decision
Industrial Workers	3-150 mg/kg/day	0.01 -0.5 mg/kg/day	No Concern
Professional Workers	3-150 mg/kg/day	0.2 - 0.9 mg/kg/day	No Concern
Consumers	1.5-150 mg/kg/day	0.06 -0.6 mg/kg/day	No Concern
Environmental (human)	1.5-150 mg/kg/day	5E-06 - 2E-05 mg/kg/day	No Concern
Environmental (water, air, soil)	PNEC water > 10 mg/L PNEC STP = 200 mg/L	water = 0.05-0.65 mg/L STP = 0.05-0.65 mg/L	No Concern

Let's make a RISK21 PLOT

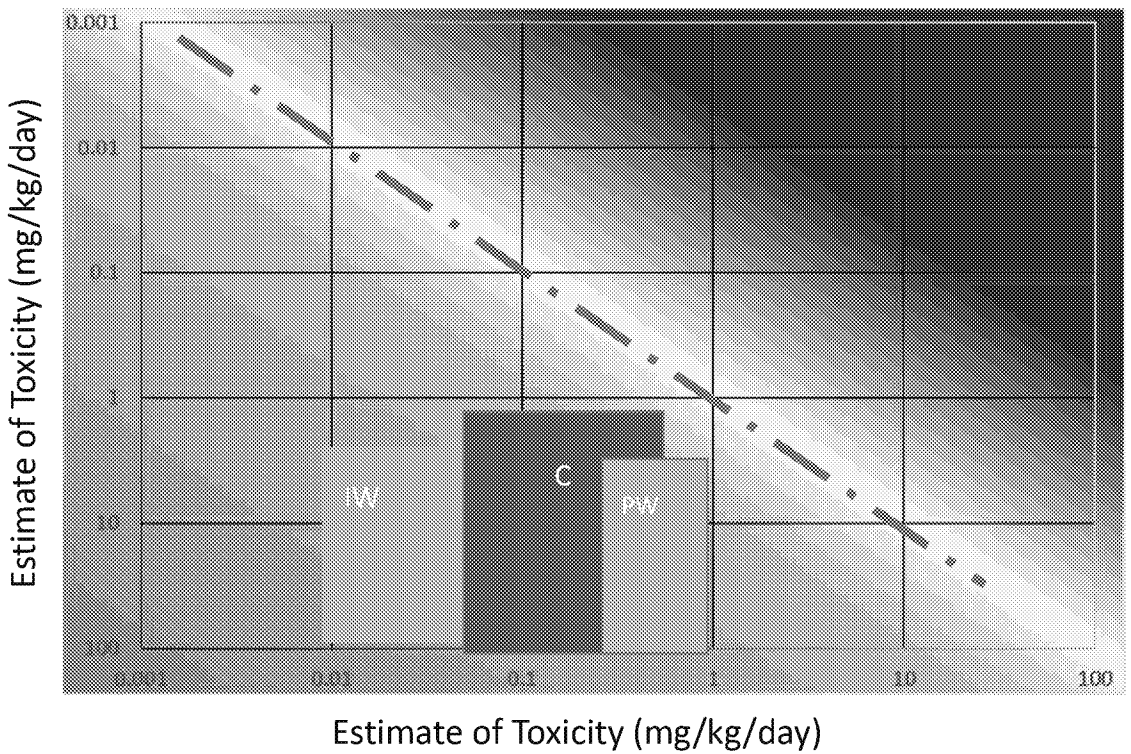
RISK21 PLOT

Combined Worker and Consumer Risk21 Plot for Example 2 (~4.5 yrs, $3.5M)

Hazard:
Based on 1 yr chronic toxicity
(1.5 – 3 mg/kg/day)

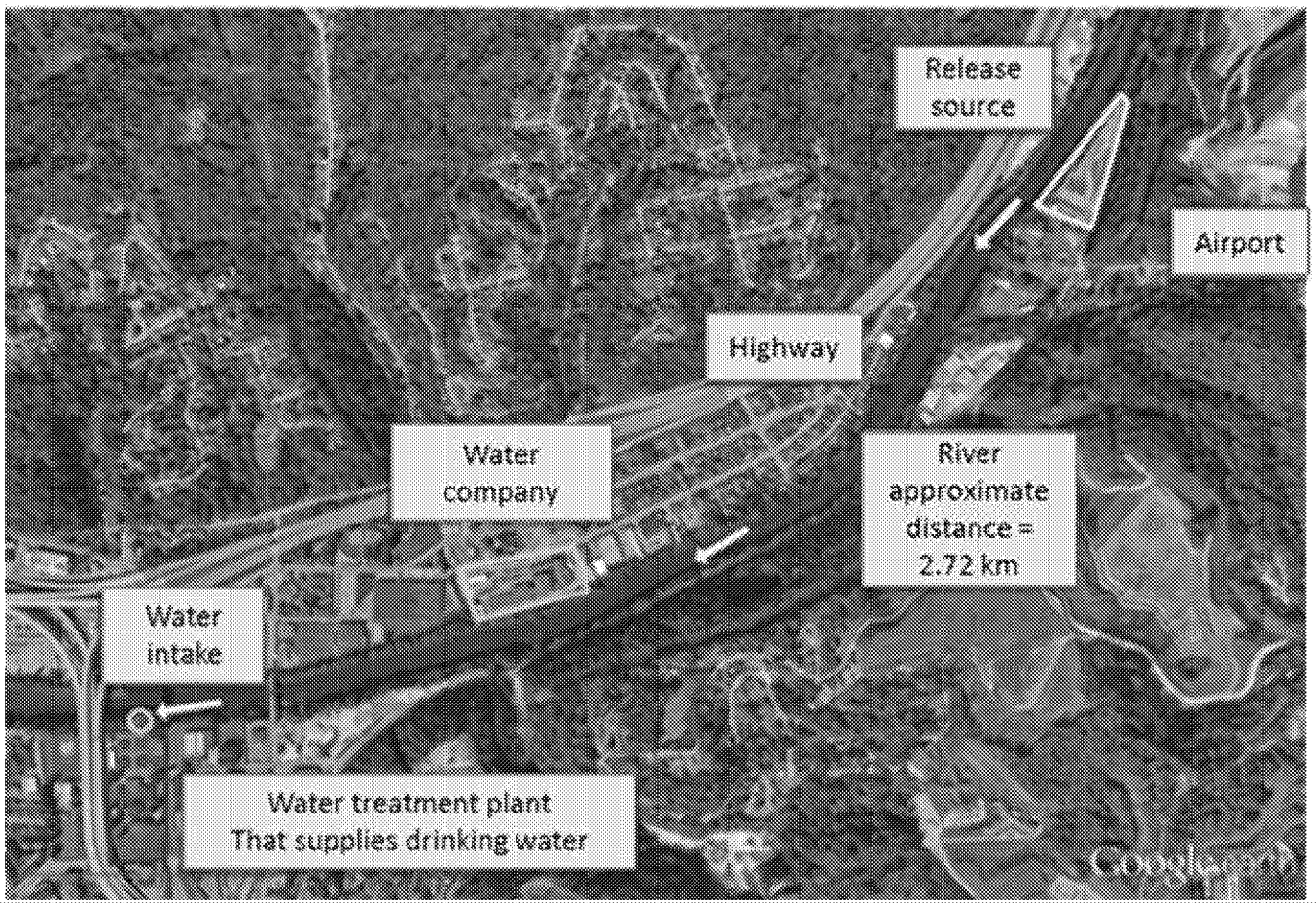
Exposure:
Based on monitoring data
(0.2-0.3 mg/kg/day)

Compare to:
-Example 1 plot with the addition of the 90 day tox test for a total of 2.5 yrs, 600K
-Example 1 plot with monitoring data or refinement of inhalation modeling and dermal penetration testing



These results show there are various approaches

Example 3: 30 Tonne accidental release into river



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Example 3

Information	Cost (USD)	Time (months)	Group
Phys-chem QSARs	$1,000	0.5	I
EFATE QSARs	$1,000	0.5	I
Acute oral	$5,000	3	II
Genotox & carcinogenicity QSAR & TTC	$3,000	0.5	I
Ecotox QSAR for short-term toxicity testing on 3 species	$3,000	0.5	I
Environmental risk assessment for 2 uses (modeling)	$10,000	0.5	II
TOTAL	$23,000	3	

Initial decision @ 1 month

Validation after 3 months

Immediately shut off water supply but need to determine when supply has low enough concentration to open again

Lots of issues when shut off water supply for residents and businesses

Example 3

Information	Cost (USD)	Time (months)	Group
Phys-chem QSARs	$1,000	hours	I
EFATE QSARs	$1,000	hours	I
Acute oral	$5,000	1	II
Genotox & carcinogenicity QSAR & TTC	$3,000	hours	I
Ecotox QSAR for short-term toxicity testing on 3 species	$3,000	hours	I
Environmental risk assessment for 2 uses (modeling)	$10,000	hours	II
TOTAL	$23,000	1	

Initial decision in hours

Validation after 1 months

Immediately shut off water supply but need to determine when supply has low enough concentration to open again

Lots of issues when shut off water supply for residents and businesses

Example 3: Risk Assessment Rationale

RESULTS	Hazard	Exposure	Decision
Oral	TTC = 0.03 mg/kg/day	addressed in environmental (human)	
Dermal	TTC = 0.03 mg/kg/day	expect to be lower than oral	
Inhalation	TTC = 0.03 mg/kg/day	addressed in environmental (human)	
Environmental (human)	TTC = 0.03 mg/kg/day	0.03 mg/kg/day based on 1ppm in water supply	No Concern if do not drink the water until reduced to 1 ppm
Environmental (aquatic species)	PNEC water 3.5 mg/L	water= 100 mg/L (based on release amount and river flow rates)	there could be some algae die offs at spill location

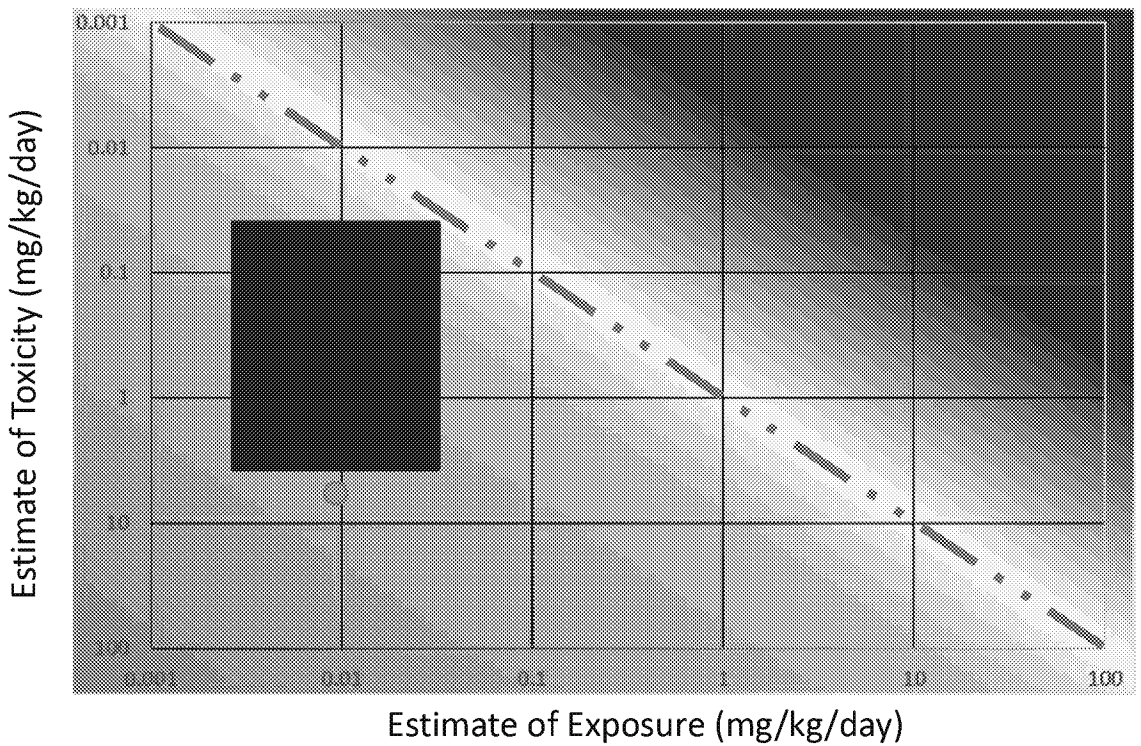
RISK21 PLOT

Risk21 Plot for Example 3 based on waiting until 1 ppm in river water

Hazard:
Based on TTC (0.03 mg/kg/day) this is a lower limit with 95% confidence

Exposure:
Modeled estimates and monitoring (0.03 mg/kg/day) this is an upper limit with 95% confidence

There is considerable uncertainty (100X)



It is all about enough precision for the decision!

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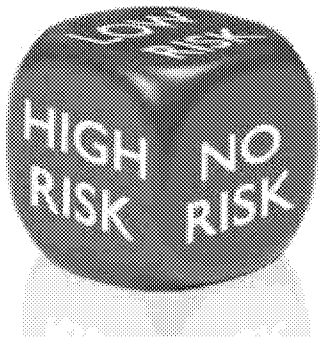
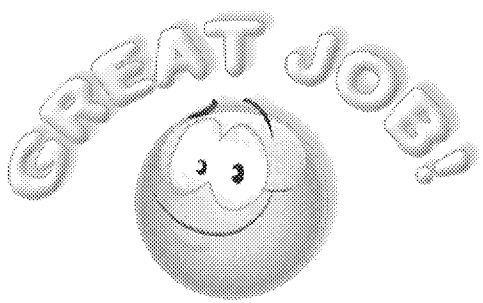
Conclusion

- Risk Assessment is a process
- There are many possible outcomes
- Involves many areas of expertise
- Keep on practicing!



Thank you for performing RiskChallenge!



Acknowledgements

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